REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-5, 7, 9-17 and 19-47 are in this case. Applicant wishes to point out that the Examiner has erroneously omitted to include in the instant Office Action (Paper No. 10) that claims 19 and 20 are pending in this case. Claims 22-45 were withdrawn under a restriction requirement as drawn to a non-elected invention. Claims 1-5, 7, 9-21, 46 and 47 have been rejected. Claims 1, 10-12, 20 and 21 have now been amended.

35 U.S.C. § 112, Second Paragraph, Rejections

The Examiner has rejected claim 10 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 10 has now been amended.

With respect to claim 10 the Examiner states that the limitation thereof "wherein said veto activity..." lacks antecedent basis therefor in base Claim 1 since base Claim 1 does not recite "veto activity". Claim 10 has now been amended to recite the limitations of a tolerance-inducing activity enhanced in each cell of said cell population to thereby overcome the Examiner's rejection. In the interest of applying consistent claims language Applicant has further chosen to amend claim 11, 12, 20 and 21 to recite the limitation of tolerance-inducing activity, instead of "veto" activity. Support for reference to "tolerance-inducing activity" of the cultured cells of the instant invention is provided on page 1, sentence starting line 24. Antecedent basis for the amendment said cell population in the amendment of claim 10 is provided in independent claim 1 from which claim 10 depends.

35 U.S.C. § 103(a) Rejections - U.S. Pat. No. 5,806,529 in view of Bachar-Lustig et al. or Mobest et al. or Vavrova et al.

The Examiner has rejected claims 1-5, 7, 9-17, 19-21, 46 and 47 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,806,529 (hereinafter the '529 Patent) in view of Bachar-Lustig *et al.*, of Mobest *et al.*, or Vavrova *et al.* The Examiner's rejections are respectfully traversed. Claims 1 and 12 have now been amended.

The Examiner states that the '529 patent teaches a method of inducing tolerance to a transplant during bone marrow transplantation comprising administering HPCs from an allogeneic donor, but that it does not teach culturing of the HPCs *ex-vivo* under conditions suitable for inducing or enhancing veto activity. The Examiner further states that Bachar-Lustig *et al.*, Mobest *et al.*, and Vavrova *et al.* teach culturing of HPCs under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPCs, and for inducing differentiation of said HPCs into CD33+ myeloid phenotype cells using the same culturing conditions as those disclosed in the instant specification. The Examiner additionally states that Mobest *et al.* and Vavrova *et al.* teach that *ex-vivo* expansion of CD34+ HPCs that would differentiate into CD33+ myeloid phenotype cells offers the possibility of various auxiliary benefits related to therapeutic transplantation of CD34+ cells.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made that CD34+ HPCs obtained and grown under the same conditions as disclosed in the instant specification would be induced to differentiate into myeloid CD33+ cells with the same functional property as HPCs recited in the instant claims absent a showing of unobvious property.

The Examiner further concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to apply the teachings of Bachar-Lustig *et al.*, Mobest *et al.* or Vavrova *et al.* to those of the '529 Patent to obtain a method of inducing tolerance to a transplant or a

method of transplanting a transplant from a donor to a recipient comprising a step of *ex-vivo* culturing HPCs under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPCs and inducing differentiation of said HPCs into CD33+ myeloid phenotype cells prior to transplantation of the transplant.

The Examiner additionally concludes that at the time the invention was made one of ordinary skill in the art would have been motivated to apply the teaching of Bachar-Lustig *et al.*, or Mobest *et al.*, or Vavrova *et al.* to those of the '529 Patent because successful *ex-vivo* expansion of CD34+ HPCs under growth conditions that would stimulate differentiation thereof into CD33+ myeloid phenotype cells prior to transplantation offers various auxiliary benefits in such a setting.

Applicant wishes to point out that, critically, despite the fact that at the time the instant invention was made there existed a long-felt need for tolerance inducing cells, in particular cultured tolerance inducing cells such as those provided by the instant invention, and despite the fact that CD33+ cells had been known in the art for at least 14 years (refer, for example, to enclosed abstract of van der Schoot *et al.*), the tolerance-inducing activity of CD33+ cells had not been uncovered.

Applicant wishes to further respectfully point out that Vavrova *et al.* teaches culturing of autologous CD34+ cells for autologous transplantation, and that as such Examiner's assertion that Vavrova *et al.* teaches growth conditions suitable for inducing or enhancing veto activity, an activity which by definition strictly applies to a non-syngeneic donor-recipient pair, is not relevant.

Therefore it is applicant's very strong opinion that it would clearly not have been obvious to the ordinarily skilled artisan at the time the instant invention was made to employ the cultured cells taught by Bachar-Lustig *et al.* or Mobest *et al.* or Vavrova *et al.* to generate cells having the same enhanced tolerance-inducing activity as the tolerance-inducing cells of the instant invention. It is therefore Applicant's very strong opinion that it would not have

been obvious to a person of ordinary skill in the art at the time the instant invention was made to apply the teachings of Bachar-Lustig *et al.*, Mobest *et al.* or Vavrova *et al.* to those of the '529 Patent to obtain a method of inducing tolerance to a transplant or a method of transplanting a transplant from a donor to a recipient comprising a step of *ex-vivo* culturing HPCs under growth conditions suitable for inducing or enhancing veto activity in at least a portion of said HPCs and inducing differentiation of said HPCs into CD33+ myeloid phenotype cells prior to transplantation of the transplant.

Nevertheless, in order to expedite prosecution of the instant application, Applicant has chosen to amend independent claims 10 and 12 to now include the limitation of culturing a donor-derived HPC population. Support for amending these claims to include this limitation is provided by the demonstration of the instant specification that the cultured HPCs of the instant invention display veto activity with respect to syngeneic but not third party stimulators in a mixed lymphocyte reaction (MLR) assay (instant specification, throughout the Experimental Results section in general, and in particular Figure 1b and the accompanying text on page 46, sentence starting on line 4).

In view of the above amendments and remarks it is respectfully submitted that claims 1-5, 7, 9-17, 19-21, 46 and 47 are now in condition for allowance. Prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: July 29, 2003

Encl.:
Abstract of van der Schoot *et al.*

Acta Haematol. 1987;78 Suppl 1:32-40.

Characterization of myeloid leukemia by monoclonal antibodies, with an emphasis on antibodies against myeloperoxidase.

van der Schoot CE, von dem Borne AE, Tetteroo PA.

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Since the last workshop on human leukocyte differentiation antigens, there are 14 well defined cluster-designated (CD) antigens which characterize myelomonocytic cells. Of these, 5 are potentially useful for myeloid leukemia typing (i.e. CD13, CD14, CD15, CD33, CD36) because they are cell lineage-specific and also expressed on immature cells. However, the reactivity of monoclonal anti-CD antibodies, directed against these antigens, with myeloblastic leukemia cells was found to be quite low. We produced monoclonal antibodies against myeloperoxidase. These antibodies react also with promyeloperoxidase, synthesized in HL-60 cell line cells. Monoclonal antimyeloperoxidase was found to be the most sensitive reagent to diagnose acute myeloid leukemia, even more sensitive than cytochemical stains (Sudan black, myeloperoxidase).

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